Thyroid peroxidase antibodies, levels of thyroid stimulating hormone and development of hypothyroidism in euthyroid subjects

Roos, A.; Links, T.P.; de Jong-van den Berg, L.T.; Gans, R.O.; Wolffenbuttel, B.H.; Bakker, S.J.

Published in:
European Journal of Internal Medicine

DOI:
10.1016/j.ejim.2010.09.001

European Journal of Internal Medicine 21 (2010) 555–559

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Thyroid peroxidase antibodies, levels of thyroid stimulating hormone and development of hypothyroidism in euthyroid subjects

Annemieke Roos [a], Thera P. Links [a], Lolkje T.W. de Jong-van den Berg [c], Rijk O.B. Gans [b], Bruce H.R. Wolffenbuttel [a], Stephan J.L. Bakker [b,*]

[a] Department of Endocrinology, Groningen University Institute for Drug Exploration, University Medical Center Groningen and University of Groningen, The Netherlands
[b] Department of Internal Medicine, Groningen University Institute for Drug Exploration, University Medical Center Groningen and University of Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands
[c] Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration, University Medical Center Groningen and University of Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 16 July 2010
Received in revised form 21 August 2010
Accepted 3 September 2010
Available online 29 October 2010

Keywords:
TPO antibodies
TSH
Euthyroidism
Hypothyroidism

ABSTRACT

Objective: Thyroid peroxidase antibodies (TPOAbs) have been found to be related to the levels of thyroid stimulating hormone (TSH) and to predict future development of thyroid failure in selected populations. We investigated these relations in a euthyroid general population.
Design: Cross-sectional investigation of the relationship of TPOAbs and levels of TSH in euthyroid subjects. Prospective investigation of the association of TPOAbs and TSH with development of hypothyroidism. Incident hypothyroidism was defined as initiation of L-thyroxine in the absence of thyreostatic medication.
Subjects: The study was performed in a random sample of 2703 participants of the PREVEND study. A total of 309 subjects were excluded from analyses, mainly because of TSH outside the reference range (0.35–4.94 mIU/l; n = 115).
Results: Mean (SD) baseline age was 47.7 (12.5) years, with 50.8% females. Prevalence of positive TPOAbs (≥12 kU/l) was 8.4%. TSH concentrations were increased in subjects with TPOAbs ($P<0.001$). During a median follow-up of 9.1 years, 15 (0.6%) subjects developed hypothyroidism (3.5% in TPOAbs positive vs. 0.4% in TPOAbs negative subjects; $P<0.001$). Female sex ($P=0.02$), and TSH ($P<0.001$) were also significantly associated with incident hypothyroidism. In multivariate analysis, TSH and TPOAbs remained independent predictors (both $P<0.001$).
Conclusions: We confirmed the positive relationship of the presence of TPOAbs with levels of TSH and showed that TPOAbs and TSH predict future development of hypothyroidism. These results are consistent with the presence of TPOAbs necessitating a compensatory increase in levels of TSH for maintenance of euthyroidism, even in the euthyroid range.

1. Introduction

Hypothyroidism, both overt and subclinical, is a common disorder, with elevated levels of serum thyrotropin (TSH) in up to almost 10% of the general population in prevalence studies [1–3]. Many of the subjects in these studies were not aware of their thyroid dysfunction. This high prevalence of undiagnosed thyroid dysfunction can have important health consequences, since hypothyroidism is associated with hypercholesterolemia [4], cardiovascular disease [5] and depression [6].

With this knowledge, assessment of TSH is now a frequently performed laboratory test. Abnormal thyroid function can be readily diagnosed in this way. It would, however, also be of particular interest if one could know which of currently euthyroid subjects are at increased risk for development of thyroid dysfunction in the near future. It is well known that higher prevalence rates of hypothyroidism are found with advancing age and in women, particularly when thyroid autoantibodies are present [1–3,7]. It has been suggested that the presence of thyroid peroxidase antibodies may serve as a marker of future thyroid failure [8]. Indeed, in a recent prospective study in a selected population of females with high risk for development of autoimmune thyroid disease, the presence of thyroid peroxidase antibodies was identified as a risk factor for future thyroid failure [9]. Moreover, in the Whickham and Busselton studies it was found that increasing values of serum TSH at baseline increased the probability of developing hypothyroidism, and that this probability was further increased when thyroid peroxidase antibodies were present [10,11]. In these studies, however, subjects with elevated levels of TSH at baseline were not excluded. It is not established whether in the euthyroid range the presence of thyroid peroxidase antibodies is

* Corresponding author. Tel.: +31 50 3613677; fax: +31 50 3619069.
E-mail address: s.j.l.bakker@int.umcg.nl (S.J.L. Bakker).

0953-6205/$ – see front matter
doi:10.1016/j.ejim.2010.09.001

associated with the levels of TSH. To the best of our knowledge, only two prospective studies investigated the value of TSH and thyroid peroxidase antibody titers in subjects with normal levels of TSH [12,13]. In these studies, however, the presence of elevated TSH levels during follow-up was assessed by screening. Screening for hypothyroidism is, however, not part of current clinical practice. The value of the presence of thyroid peroxidase antibodies as a risk factor for future development of clinical thyroid failure in currently euthyroid subjects of the general population remains therefore to be established.

Our aim was to investigate, in an unselected sample of euthyroid subjects within the general population, the relationship of the presence of thyroid peroxidase antibodies (TPOAbs) with the levels of TSH within the normal reference range. We also aimed to prospectively investigate whether the presence of TPOAbs and levels of TSH predict incident clinical hypothyroidism – defined as prescription of L-thyroxine by a general practitioner or internist — in the same euthyroid subjects.

2. Methods

2.1. Study population and design

The database used for this study consisted of a random sample of 2703 participants of the PREVEND (Prevention of REnal and Vascular ENd stage Disease) study, all inhabitants, aged 28 to 75 years, of the city of Groningen, a middle-sized city in the northern part of the Netherlands. Pregnant women were excluded from this study. The protocol of the PREVEND study has been described elsewhere [14]. In short, this study prospectively investigates the natural course of renal and cardiovascular disease in a large cohort drawn from the general population.

At baseline, blood was drawn to assess thyroid function and TPOAbs status, after which subjects were prospectively followed. TPOAbs were considered positive when ≥12 kU/l, which is the cut-off point recommended by the manufacturer of the assay (Abbott Laboratories, Abbott Park, IL 60064, USA; kit number 5F57). For our analyses, we only studied euthyroid subjects according to a TSH level within our laboratory's reference range (0.35–4.94 mIU/l). We excluded a total number of 309 subjects: those with – at baseline – a TSH above the laboratory's reference range (n = 52) and those with – at baseline – a TSH below the laboratory's reference range (n = 63), as well as subjects of whom TPOAbs status was missing (n = 4). Subjects of whom no follow-up of pharmacy data (with information about prescription of drugs, including thyroid medication) was available (n = 92) were also excluded. We further excluded subjects who were taking thyroid medication (both L-thyroxine and thyrostatic drugs; n = 37) and/or medications that may affect thyroid function tests at baseline (namely oral glucocorticoids, lithium and/or amiodarone [15]; n = 56). Subjects that developed hyperthyroidism during follow-up were also excluded from analyses (n = 5), leaving 2394 subjects eligible for analyses. The Netherlands is considered to be a country with a sufficient intake of dietary iodine, with a median urinary iodine excretion level of 154 μg/l [16].

The study was approved by the local medical ethical committee. All participants gave written informed consent.

2.2. Assays and measurements

Serum samples were stored at −20 °C until analysis. Serum TSH was assessed using a microparticle enzyme immunoassay (Architect, Abbott Laboratories, Abbott Park, IL 60064, USA). FT4 and FT3 concentrations were also assessed using a microparticle enzyme immunoassay (AxSYM, Abbott Laboratories, Abbott Park, IL 60064, USA). Serum thyroperoxidase antibodies (TPOAbs) were assessed using a microparticle enzyme immunoassay (AxSYM) for the quantitative measurement of immunoglobulin G (IgG) class antibodies.

Body Mass Index (BMI) was calculated as body weight (kilogram) divided by the square of body height (meter).

2.3. Definition of incident hypothyroidism

Incident hypothyroidism was defined as initiation of L-thyroxine therapy in the absence of thyreostatic medication. The practice guidelines 'Thyroid disorders' from the Dutch College of General Practitioners and The Netherlands Association of Internal Medicine recommend start of treatment for hypothyroidism if TSH exceeds 12 mIU/l [17,18]. It is not recommended to treat subjects with TSH ≤ 12 mIU/l, which is considered subclinical hypothyroidism. Dutch physicians adhere well to these guidelines [19]. The PREVEND participants were asked at which pharmacy they collected their prescription medication. At baseline and during follow-up, pharmacy records were collected at community pharmacies. Because Dutch patients usually register at a single community pharmacy, use of pharmacy records provides an individual listing of prescribed drugs for each PREVEND participant [20,21]. The pharmacy data contain, among others, the name of the drug, number of units dispensed, prescribed daily dose, the date the drugs were obtained, and Anatomical Therapeutical Chemical classification code of the drug.

2.4. Statistical analysis

SPSS 12 (SPSS, Inc., Chicago, IL) and Excel (Microsoft Corp., Redmond, WA) were used for data analysis. Data are expressed as mean (SD) or median [interquartile range] when appropriate. Statistical comparisons were performed by means of independent-sample *t* tests for data with a normal distribution, Mann–Whitney *U* tests for data with a skewed distribution and Chi-square tests for percentages. Logistic regression analyses were performed for assessment of associations of TPOAbs status with age and TSH. Cox-regression analyses were performed for assessment of associations of age, sex, smoking, thyroid function parameters and log-transformed TPOAbs with incidence of hypothyroidism, both univariately and multivariately. Variables retained in the final multivariate model were selected by a stepwise backward procedure. P values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Population characteristics according to TPOAbs status are shown in Table 1. Median [interquartile range] TPOAbs titer in TPOAbs positive subjects was 85 [31-243] kU/l. Age, percentage of females, TSH and BMI were significantly higher in TPOAbs positive subjects compared to TPOAbs negative subjects.

Prevalence of positive TPOAbs was 8.4% (11.9% vs. 4.8% for females and males respectively; P < 0.001). This percentage increased with age (P = 0.006), with highest prevalence (18.7%) in women aged 60–69 years. The prevalence of positive TPOAbs according to quartiles of

Table 1
Baseline characteristics (n = 2394), according to TPOAbs status.

	TPOAbs −	TPOAbs +	P value
N (%)	2193 (91.6)	201 (8.4)	
Age (year)	47 (12)	50 (13)	0.006
Gender (females)	49%	72%	<0.001
BMI (kg/m^2)	25.8 (4.2)	26.6 (4.3)	0.02
Smoking (n/% yes)	914 (42)	75 (37)	0.21
TSH (mIU/l)	1.33 [0.96–1.84]	1.73 [1.22–2.56]	<0.001
FT4 (pmol/l)	12.8 ± 2.3	12.6 ± 1.8	0.11
FT3 (nmol/l)	3.8 ± 1.7	3.6 ± 0.7	0.15

Data are given as mean (SD) or median [interquartile range].

TSH ranged from 4.5% in the lowest to 14.7% in the highest quartile of TSH in the euthyroid range (P<0.001, Fig. 1). Median [interquartile range] TSH for TPOAbs positive subjects was 1.73 [1.22–2.56] mIU/l, compared to 1.33 [0.96–1.84] mIU/l in TPOAbs negative subjects (P<0.001).

3.2. Relationship of positive TPOAbs and future thyroid dysfunction

Median [interquartile range] follow-up was 9.1 [9.0–9.2] years. During follow-up, incidence of hypothyroidism was much lower in subjects in the lowest quartiles of TSH than those in the highest quartile (1 (0.2%), 2 (0.3%), 2 (0.3%) and 10 (1.7%) respectively, P<0.001). A Kaplan–Meier plot for the lowest three quartiles vs. the highest quartile is shown in Fig. 2. Incidence of hypothyroidism was significantly lower in TPOAbs negative subjects than in TPOAbs positive subjects: 8 out of 2193 TPOAb negative subjects vs. 7 out of 201 TPOAb positive subjects started L-thyroxine (0.4% vs. 3.5%; P<0.001). A Kaplan–Meier plot of the respective incidences is shown in Fig. 3.

Results of univariate and multivariate Cox-regression analyses are shown in Table 2. In univariate analyses, female sex appeared also predictive of development of hypothyroidism, in addition to TSH and TPOAbs. The association of FT4 was borderline significant. In subsequent multivariate analyses, only TSH and TPOAbs remained as significant independent predictors of incident hypothyroidism.

4. Discussion

We found a cross-sectional positive association between the presence of TPOAbs and the levels of TSH within the euthyroid range. These results are consistent with the presence of TPOAbs necessitating a compensatory increase in levels of TSH for maintenance of euthyroidism, even in the euthyroid range. We also found that TSH and TPOAbs predict development of hypothyroidism in a general population of subjects with all normal levels of TSH at baseline. Incidence of hypothyroidism during 9 years of follow-up was significantly higher in subjects with positive TPOAbs at baseline compared to TPOAbs negative subjects. We demonstrated that both TPOAbs and TSH level are independent predictors of hypothyroidism, even in subjects with a TSH level within the normal laboratory's reference range.

We found a cross-sectional association between the presence of TPOAbs and increasing levels of TSH within the euthyroid range. This finding, in combination with the presence of TPOAbs and the levels of TSH as independent predictors of future development of thyroid failure, strongly suggests that TSH levels – even though they are still in what is considered the normal range – in subjects with TPOAbs would have been lower if they would not have had TPOAbs. Apparently, the presence of TPOAbs frequently sets a subject in a compensated state in which somewhat higher levels of TSH – although still in the reference range – are necessary for the thyroid to produce enough thyroid hormone to maintain euthyroidism. This finding is consistent with earlier studies by Jensen et al. and Hollowell et al., where the presence of TPOAbs was not only found to be associated with a higher frequency of levels of TSH outside the reference range, but also with a tendency for higher levels of TSH within the reference range [2,22].

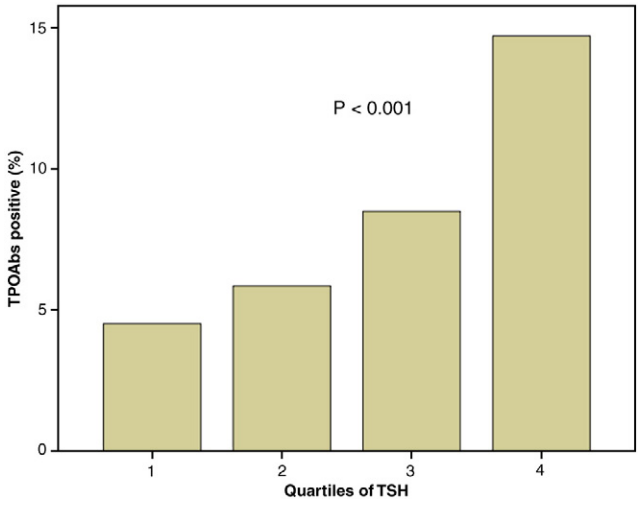

Fig. 1. Prevalence of positive TPOAbs for quartiles of TSH within the normal reference range (n = 2394). TSH ranged from 0.35 to 0.97 mIU/l in quartile 1, from 0.97 to 1.36 in quartile 2, from 1.36 to 1.89 in quartile 3 and from 1.89 to 4.85 in quartile 4.

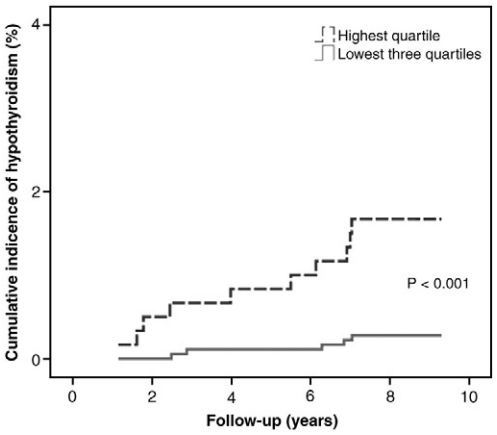

Fig. 2. Kaplan–Meier plot for incidence of hypothyroidism according to TSH.

Our findings fit well with results of a recently published prospective study in a high risk population of female relatives of patients with autoimmune thyroid disease, in which the presence of TPOAbs and high normal levels of TSH levels were found to predict future development of overt thyroid disease [9]. Our prospective study confirms the importance of TPOAbs as a marker for future thyroid disease and extends it to the general population. To the best of our knowledge, only two earlier prospective studies investigated the value of TSH and TPOAb titers in subjects with normal levels of TSH [12,13]. One study, however, only included middle-aged women and the other was performed in an area in which mild iodine deficiency is very common. Iodine deficiency is virtually absent in the Netherlands [16]. Other studies were performed in subjects with established subclinical hypothyroidism and demonstrated the predictive value of thyroid antibodies for development of overt hypothyroidism in these subjects [23,24]. In the Whickham and Busselton studies it was found that increasing values of serum TSH at first survey increased the

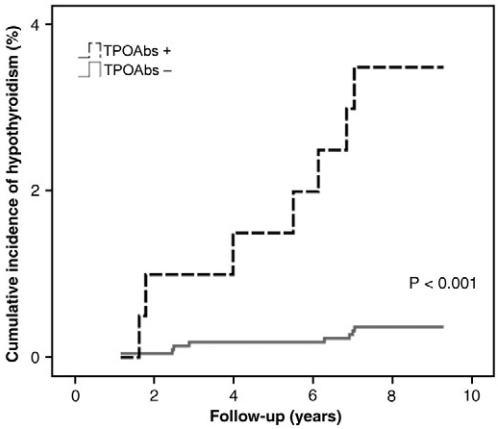

Fig. 3. Kaplan–Meier plot for incidence of hypothyroidism according to TPO status.

Table 2
Univariate and multivariate Cox-regression analyses for determinants of incident hypothyroidism.

	Univariate analyses			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.98	0.65–1.47	0.93	–	–	–
Sex	6.33	1.43–28.03	0.02	–	–	–
Current smoking	0.71	0.24–2.07	0.52	–	–	–
Ex-smoking	0.83	0.27–2.61	0.75	–	–	–
TSH	3.19	2.09–4.88	<0.001	2.41	1.53–3.79	<0.001
FT4	0.78	0.58–1.03	0.08	–	–	–
FT3	0.92	0.47–1.81	0.80	–	–	–
log TPOAbs	3.84	2.40–6.15	<0.001	2.87	1.67–4.90	<0.001

probability of developing hypothyroidism, and that this probability was further increased when TPOAbs were present [10,11]. In these studies, however, subjects with elevated levels of TSH at baseline were not excluded. Our results extend the findings of these studies with the notion that even variation of levels of TSH within what is considered the normal range is important for prediction of development of hypothyroidism.

The pathophysiologic process behind the relationship of TPOAbs prevalence and future thyroid disease is complex and not completely understood [25]. Thyroid peroxidase (TPO) is not only known to be the primary enzyme in the synthesis of thyroid hormone, it also serves as a major autoantigen [26]. Moreover, it has been hypothesized that TPOAbs should not be viewed as one entity since their pathogenic potential might be influenced depending on which epitope of TPO they are binding to [27]. The presence of TPOAbs is characteristic for autoimmune thyroid diseases [28], both in hypothyroidism (Hashimoto's thyroiditis) and (Graves') hyperthyroidism. The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors [7]. The antibodies are mainly produced by a lymphocytic infiltrate in the thyroid gland [29], with a significant correlation between the degree of this lymphocytic infiltration and the titer of microsomal antibodies [30]. In combination with the demonstrated higher prevalence of positive TPOAbs with increasing TSH concentrations, even in euthyroidism, the presence of TPOAbs can thus be regarded as a marker for increased risk of future thyroid failure.

In recent years there have been considerable discussion and disagreement regarding the upper normal TSH concentration [31,32]. Subclinical hypothyroidism, an elevated serum TSH level in combination with normal FT4 concentrations, has been found to be associated with ischemic heart disease [33,34]. However, randomized controlled trials that show that levothyroxine replacement therapy for subclinical hypothyroidism results in improved survival or decreased cardiovascular morbidity are lacking [35]. Thus, the relevance of our findings from the perspective of cardiovascular protection has not yet been established. From the perspective of health care, however, it is very relevant. Hypothyroidism is a prevalent disorder, which develops slowly, and acknowledgment of symptoms is frequently difficult. Therefore, many guidelines advise screening of subjects in case of vague complaints [36]. Moreover, aggressive case finding is recommended in pregnant women, women older than 60 years, and others at high risk for thyroid dysfunction, although consensus about screening strategies is lacking [36,37]. It is not known for how long a normal TSH can be trusted as certification of sustained euthyroidism. Our results suggest that sustainability of a normal TSH is much higher in people with TSH in the lower range of normal concentrations and in people with the absence of TPOAbs. Future studies will have to be performed to designate more detailed screening strategies.

There are some limitations to our study. We have underestimated incidence of hypothyroidism since no repeated measurements of all subjects in our study were performed. Indeed, incidence of hypothyroidism in our study (0.015%/year) was much lower than incidence found in a large Dutch study among general practitioners (0.12%/year) [38] and in the earlier mentioned other follow-up studies [12,13].

Instead, incident hypothyroidism was defined as prescription of L-thyroxine by general practitioners and internists. These physicians were unaware of baseline laboratory results. Therefore, only subjects who visited their doctor with complaints were detected. Currently, in many countries no routine screening programs for thyroid function testing are running. For this reason, however, our study is in keeping with the daily practice of general practitioners and internists and presents the relevance of knowledge of results of an assay for TPOAbs for clinical practice. However, this is more likely to result in underappreciation of the effects of TPOAbs and levels of TSH as predictors of development of thyroid failure rather than overappreciation. An important strength of our study is the availability of pharmacy data, which is a highly reliable measure of prescribed drugs [20,21], which also allowed us to perform time-to-event analyses for development of thyroid failure.

In conclusion, in a cross-sectional study we demonstrated a relation of the presence of TPOAbs with the levels of TSH within the euthyroid range. This is highly suggestive of the presence of TPOAbs to necessitate a compensatory increase in the levels of TSH for maintenance of euthyroidism. Moreover, in euthyroid subjects in a general population we have demonstrated that TPOAbs level and TSH level are both independent predictors for future hypothyroidism, even when TSH is still within the laboratory reference range. Although our results need to be confirmed in studies with repeated measurements of thyroid status, our results strongly suggest that TPOAbs and levels of TSH can be used as a tool for identifying subjects at risk for developing overt hypothyroidism in the general population.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Learning points

- There is a positive relationship of the presence of TPOAbs with the levels of TSH, even in the euthyroid range.
- Both TPOAbs and TSH independently predict future development of hypothyroidism, even in the euthyroid range.

References

[1] Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160(4):526–34.
[2] Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87(2):489–99.
[3] Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977;7(6):481–93.
[4] Duntas LH. Thyroid disease and lipids. Thyroid 2002;12(4):287–93.
[5] Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003;88(6):2438–44.
[6] Esposito S, Prange Jr AJ, Golden RN. The thyroid axis and mood disorders: overview and future prospects. Psychopharmacol Bull 1997;33(2):205–17.
[7] Roberts CG, Ladenson PW. Hypothyroidism. Lancet 2004;363(9411):793–803.
[8] Strieder TG, Prummel MF, Tijssen JG, Endert E, Wiersinga WM. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. Clin Endocrinol (Oxf) 2003;59(3):396–401.
[9] Strieder TG, Tijssen JG, Wenzel BE, Endert E, Wiersinga WM. Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of

patients with autoimmune thyroid disease using the Thyroid Events Amsterdam (THEA) score. Arch Intern Med 2008;168(15):1657–63.
[10] Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995;43(1):55–68.
[11] Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010;95(3):1095–104.
[12] Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, et al. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: associations with serum lipids. Clin Endocrinol (Oxf) 1993;39(3):275–80.
[13] Li Y, Teng D, Shan Z, Teng X, Guan H, Yu X, et al. Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 2008;93(5):1751–7.
[14] Pinto-Sietsma SJ, Janssen WM, Hillege HL, Navis G, de Zeeuw D, De Jong PE. Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. J Am Soc Nephrol 2000;11(10):1882–8.
[15] Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med 1995;333(25): 1688–94.
[16] Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-Ter Schiphorst MC. A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol 2001;144(6):595–603.
[17] Muller AF, Berghout A, Wiersinga WM, Kooy A, Smits JW, Hermus AR. Thyroid function disorders—Guidelines of the Netherlands Association of Internal Medicine. Neth J Med 2008;66(3):134–42.
[18] van Lieshout J, Wessels P, van Rijswijk E, Boer AM, Wiersma A, Goudswaard AN. Summary of the practice guideline 'Thyroid disorders' (first revision) from the Dutch College of General Practitioners. Ned Tijdschr Geneeskd 2007;151(51): 2829–32.
[19] Lugtenberg M, de Vries P, Evertse A, Zegers-van Schaick J, Westert G, Burgers J. Welke barrieres ervaren huisartsen bij de toepassing van aanbevelingen uit NHG-standaarden? Huisarts Wet 2010;53(1):13–9.
[20] Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50(5):619–25.
[21] Monster TB, Janssen WM, De Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11(5):379–84.
[22] Jensen E, Hyltoft PP, Blaabjerg O, Hansen PS, Brix TH, Kyvik KO, et al. Establishment of a serum thyroid stimulating hormone (TSH) reference interval in healthy adults. The importance of environmental factors, including thyroid antibodies. Clin Chem Lab Med 2004;42(7):824–32.
[23] Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab 2002;87(7):3221–6.
[24] Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA 1987;258(2):209–13.
[25] McLachlan SM, Rapoport B. Thyroid peroxidase as an autoantigen. Thyroid 2007;17(10):939–48.
[26] McLachlan SM, Rapoport B. The molecular biology of thyroid peroxidase: cloning, expression and role as autoantigen in autoimmune thyroid disease. Endocr Rev 1992;13(2):192–206.
[27] Nielsen CH, Brix TH, Gardas A, Banga JP, Hegedus L. Epitope recognition patterns of thyroid peroxidase autoantibodies in healthy individuals and patients with Hashimoto's thyroiditis. Clin Endocrinol (Oxf) 2008;69(4):664–8.
[28] Prummel MF, Wiersinga WM. Thyroid peroxidase autoantibodies in euthyroid subjects. Best Pract Res Clin Endocrinol Metab 2005;19(1):1–15.
[29] McLachlan SM, Pegg CA, Atherton MC, Middleton SL, Dickinson A, Clark F, et al. Subpopulations of thyroid autoantibody secreting lymphocytes in Graves' and Hashimoto thyroid glands. Clin Exp Immunol 1986;65(2):319–28.
[30] Yoshida H, Amino N, Yagawa K, Uemura K, Satoh M, Miyai K, et al. Association of serum antithyroid antibodies with lymphocytic infiltration of the thyroid gland: studies of seventy autopsied cases. J Clin Endocrinol Metab 1978;46(6):859–62.
[31] Brabant G, Beck-Peccoz P, Jarzab B, Laurberg P, Orgiazzi J, Szabolcs I, et al. Is there a need to redefine the upper normal limit of TSH? Eur J Endocrinol 2006;154(5): 633–7.
[32] Hamilton TE, Davis S, Onstad L, Kopecky KJ. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. J Clin Endocrinol Metab 2008;93(4):1224–30.
[33] Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000;132(4): 270–8.
[34] Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab 2004;89(7):3365–70.
[35] Villar HC, Saconato H, Valente O, Atallah AN. Thyroid hormone replacement for subclinical hypothyroidism. Cochrane Database Syst Rev 2007;3:CD003419.
[36] Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160(11):1573–5.
[37] Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291(2):228–38.
[38] Van der Linden MW, Westert GP, de Bakker DH, Schellevis FG. The Second Dutch National Survey of General Practice. 2004. Utrecht, the Netherlands, NIVEL.